REMARKS

Claims 1, 7, 9-11, 14-86, 88-90, 93, 95-105, 107-117, 119-127, 129-139 and 141-145 are pending in the present application. Claims 14-84, 96, 107-109, 111-117 and 119-121 were previously withdrawn from consideration as drawn to a non-elected invention. Claims 2-6, 8, 12, 13, 87, 91, 92, 94, 106, 118, 128, and 140 were previously cancelled. By virtue of this response, claims 122-126, 134-135, and 137-139 have been cancelled, claims 1, 85-86, 90, 127, and 136 have been amended and no new claims have been added. Accordingly, claims 1, 7, 9-11, 85-86, 88-90, 93, 95, 97-105, 110, 127, 129-133, 136, and 141-145 are currently under consideration. Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

Claims 1, 85, and 86 have been amended to narrow the range of the TRPV1 agonist or capsaicin to about 10% (w/v) to about 30% (w/v). The description of the first and second penetration enhancers have been reworded, and benzyl alcohol was added to the list of second penetration enhancers. Support for the addition of benzyl alcohol to the second penetration enhancers may be found throughout the specification, for instance in paragraph [0103]. Claim 1 has been further amended to recite "wherein a single application of the liquid formulation results in pain relief for at least two weeks", support for which may be found throughout the specification, for instance in paragraph [0163]. Claim 90 has been amended to replace "95%" with "90%". Claim 127 has been amended to depend from claim 1. Claim 136 has been amended to depend from claim 85 and the number "6%" has been replaced with "10%". No new matter has been added and reconsideration of the claims is respectfully requested in view of the amendments to the claims and the arguments below.

Information Disclosure Statement

Applicants acknowledge that the Information Disclosure Statements submitted on January 4, 2010 and July 23, 2010 which were filed after the mailing date of the previous Office Action on December 28, 2009 are in compliance with the provisions of 37 CFR 1.97. Accordingly, they have been considered by the Examiner.

Claims Rejections – 35 USC § 112

Claim 90 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Office Action states that the combination of the penetration enhancers cannot be more than 94% of the formulation since claim 1 recites that the formulation comprises 6-60% of a TRPV1 agonist. Claim 90 previously recited that the combination of first and second penetration enhancers comprise at least 95% of the liquid formulation

Claim 1 and claim 90 have been amended such that claim 90 discloses a formulation comprising between about 10% (w/v) to about 30% (w/v) or a TRPV1 agonist, optional additional components comprising not more than 5% (w/v) and a first and second penetration enhancer comprising at least 90% of the liquid formulation. Accordingly, Applicants request that the rejection be withdrawn.

Claims Rejections – 35 USC § 103

Claims 1, 7, 9, 10-11, 85-86, 88-90, 93, 97-99, 122-127, 129-139 and 141-145 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combined disclosures of Robbins US 2001/0002406 hereafter '406 in view of Patel et al. (USPN 4,863,970 hereafter '970) and Jun et al. (USPN 6,299,902 hereafter '902). The Applicant respectfully disagrees with the rejection for at least the following reasons.

The '406 application fails to disclose a liquid formulation or a method of applying a liquid formulation

The Examiner cites application '406 as the primary reference against the invention and alleges that the disclosed formulation can be applied in a liquid form in a reservoir type patch device and refers to paragraph [0017]. Contrary to the Examiner's interpretation, no mention is made of a liquid formulation or applying a liquid formulation; instead, the '406 application is directed to compositions and methods of using a patch.

Paragraph [0017] discloses a reservoir type patch consisting of "a polypropylene/polyester impervious backing member heat-sealed to a polypropylene porous/permeable membrane with a reservoir therebetween". Use of this patch is disclosed in Example 1 which describes the delivery of capsaicin via a "patch for 60 minutes". In contrast, the methods of the instant claims recite a method comprising topically applying a "liquid formulation" to a surface of a mammal. Thus, '406 does not disclose the step of applying a liquid formulation to a surface of the mammal as recited in the claim.

Application '406 does not even suggest a liquid formulation, and does not provide sufficient basis for an obviousness rejection. Applicants respectfully submit that the Office Action fails to establish a *prima facie* case of obviousness for at least this reason; accordingly this rejection should be withdrawn.

The '406 application fails to disclose a liquid formulation comprising a TRPV1 agonist, first and second penetration enhancers, and not more than 5% (w/v) of optional additional components

According to MPEP § 2143.03, all words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970) The instant claims are narrowly drawn to a composition comprising a TRPV1 agonist, at least a first and second penetration enhancer, and optional additional components comprising not more than 5% (w/v) of the liquid formulation, i.e., the liquid formulation is mostly a TRPV1 agonist and penetration enhancers.

It appears that the Office Action fails to address this limitation entirely. The '406 application discloses a reservoir type patch consisting of "a polypropylene/polyester impervious backing member heat-sealed to a polypropylene porous/permeable membrane with a reservoir therebetween" which clearly does not provide a basis to reject the liquid formulation of the instant claims. In order to rely on '406, all the claim limitations, including the limitation directed toward optional additional components comprising not more than 5% (w/v), must be met. Since the cited

reference does not teach or disclose this claim limitation, for at least this reason, this rejection should be withdrawn.

The combination of the '406 application and the '970 patent fails to provide the recited first penetration enhancer

The present claims recite a formulation comprising, among other things, at least a first penetration enhancer and a second penetration enhancer, wherein the first penetration enhancer is propylene glycol or diethylene glycol monoethyl ether and the second penetration enhancer is selected from the group consisting of ethyl oleate, oleic acid, oleyl alcohol, benzyl alcohol and menthone.

The Examiner acknowledges that the '406 application is silent to the penetration enhancers of the instant claims. The Examiner relies on the '970 patent, alleging that it discloses oleic acid, oleyl alcohol and propylene glycol, and points to the abstract (Office Action, page 4). Although the abstract discloses oleic acid and oleyl alcohol, it does not disclose propylene glycol or diethylene glycol monoethyl ether.

According to MPEP § 2143(A), in order reject a claim based on the combination of prior art elements, the Office Action must articulate at least a finding that the prior art included each element claimed. In applying this standard to the present facts, the Examiner must show that the combination of application '406, and the secondary reference, patent '970, discloses each element claimed, specifically the first penetration enhancer of propylene glycol or diethylene glycol monoethyl ether. The '406 application fails to disclose a first penetration enhancer of propylene glycol or diethylene glycol monoethyl ether as recited, and patent '970 fails to cure this deficiency. Without such a showing, the Examiner has not established a *prima facie* case of obviousness; accordingly, this rejection should be withdrawn for at least this reason.

The last sentence of the abstract recites *poly*propylene glycol for use as a diluent. In the event that the Examiner is equating the diluent polypropylene glycol to propylene glycol as a penetration enhancer, the Applicant points out that these are two very different substances having

different chemical and physical properties, such as melting point, boiling point, viscosity, and density. *Poly*propylene glycol is a polymer typically having a substantially greater molecular weight than propylene glycol, which is not a polymer. The polymer comprises a chain of monomer units connected by ether linkages, whereas propylene glycol has no ether linkage. A person having ordinary skill in the art would not expect the same results by substituting *poly*propylene glycol diluent for a penetration enhancer such as propylene glycol.

The claimed composition has unexpected advantages over the patch

Even if a *prima facie* case of obviousness was established, the Applicant presents evidence and arguments rebutting the *prima facie* case, MPEP 2145. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)

The Applicant submits herewith a declaration by Geertrui F. Vanhove, M.D., Ph.D. under 37 C.F.R. § 1.132 showing unexpected results of the claimed invention. The declaration compares the effects of applying a liquid capsaicin formulation, Formulation A, and a capsaicin patch, Formulation B, to subjects and measuring the epidermal nerve fiber (ENF) density after 7 days of treatment. Unexpectedly, significant reductions in ENF density were observed after only 5 minutes of liquid application and was similar to reductions after 60 minutes of patch application. Moreover, this reduction in ENF density with the liquid formulation surprisingly occurred with less pain than produced by the application of the patch formulation. For instance, at 60 minutes post application, the pain score of the liquid formulation is half of the pain score of the patch. Thus, declaration provides evidence that a 5 minute application of the liquid formulation is similarly effective to a 60 minute application of the capsaicin patch and results in less pain than the patch treatment, which is surprising and unexpected.

The claimed composition has unexpected advantages over other formulations

The present claims recite formulations wherein the first penetration enhancer is propylene glycol or diethylene glycol monoethyl ether and the second penetration enhancer is

selected from the group consisting of ethyl oleate, oleic acid, oleyl alcohol, benzyl alcohol and menthone. The Examiner contends that it would have been obvious to combine the penetration enhancers of patent '970 with application '406 "in order to provide enhanced drug transmission". However, the Examiner has not provided a reason why the selected penetration enhancers would have been obvious over the '970 reference.

As shown in the declaration, certain combinations of penetration enhancers have surprising and unexpected benefits over other formulations. For instance ENF density was reduced by 50% for Formulation A (propylene glycol, oleyl alcohol) and Formulation D (propylene glycol, oleic acid and benzyl alcohol), but only 6 % for Formulation E (DGME). Thus, the evidence shows that not all penetration enhancers result in the same efficacy, and it would not have been obvious to a person having ordinary skill in the art to claim the specific penetration enhancers and their combination as recited in the claims.

The rebuttal evidence shows that the prior art references fail to disclose or render obvious the claimed compositions and preclude a conclusion of obviousness of the claimed formulations and method of use. For at least these reasons this rejection should be withdrawn.

Remaining 103(a) rejections

A. The Examiner has acknowledged that the '406 application does not disclose a microemulsion topical formulation and relies on patent '902 to cure this deficiency. However, patent '902 does not cure the deficiencies of the combination of '406 and '970 as discussed above. This rejection should be withdrawn.

B. Claims 85-96 and 98-103 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combined disclosures of Robbins US 2001/0002406 hereafter '406 in view of Patel et al. (USPN 4,863,970 hereafter '970) and Hahn et al. (USPN 5,756,107 hereafter '107). Hahn '107 does not cure the deficiencies of the combination of '406 and '970 as discussed above. This rejection should be withdrawn.

C. Claims 85-96, 98, 104-105 and 110 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combined disclosures of Robbins US 2001/0002406 hereafter '406 in view of Patel et al. (USPN 4,863,970 hereafter '970) and Beerse et al. (USPN 5,968,539 hereafter '539). Beerse '539 does not cure the deficiencies of the combination of '406 and '970 as discussed above. This rejection should be withdrawn.

Response to Arguments

Applicants acknowledge that the rejection of claims 1, 7, 9-11, 85-86, 88-90, 93, 95, 97-105, 110, 122-127, 129-139 and 141-145 under 35 U.S.C. § 102(b) have been withdrawn in view of Applicant's arguments filed on March 24, 2010.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Any remarks in support of patentability of one claim should not be imputed to any other claim, even if similar terminology is used. Additionally, any remarks referring to only a portion of a claim should not be understood to base patentability on that portion; rather, patentability must rest on each claim taken as a whole. Applicant respectfully traverses each of the Examiner's rejections and each of the Examiner's assertions regarding what the prior art shows or teaches, even if not expressly discussed herein. Although amendments have been made, no acquiescence or estoppel is or should be implied thereby. Rather, the amendments are made only to expedite prosecution of the present application, and without prejudice to presentation or assertion, in the future, of claims on the subject matter affected thereby.

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child, or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.524522001300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 17, 2010

Respectfully submitted,

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